Decision Memo for Cryosurgery Ablation for Prostate Cancer (CAG-00031N)

Decision Summary

(1) Approve coverage as primary treatment for clinically localized prostate cancer. (Stages T1-T3)

(2) Continue noncoverage for salvage therapy for local failures after radical prostatectomy, external beam irradiation, and brachytherapy

The Cover Issues Manual 35-96 will be modified to reflect this change in policy.

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Decision Memo

TO: File: Cryosurgery Ablation of the Prostate
CAG Control No. 1998-00031N

FROM:

Grant P. Bagley, MD, JD
Director, Coverage and Analysis

John J. Whyte, MD, MPH
Medical Officer, Coverage and Analysis

RE: National Coverage Decision

DATE: February 1, 1999

This memo serves three purposes: (1) reviews the history of coverage policies for cryosurgery ablation of the prostate as a treatment for prostate cancer (2) analyzes recent developments including new scientific data; (3) delineates the reasoning in issuing a national coverage decision for localized prostate cancer. The decision in this memo is based upon a thorough review of all available scientific literature (both published and unpublished), lengthy discussions with the two manufacturers (Cryomedical Sciences and Endocare), numerous meetings and phone calls with Covance and members of the American Urological Association as well as the Society of Urological Cryosurgeons, discussions with various carrier medical directors and the urology work group, consultation with medical experts in urology including those who perform the procedure as well as those who do not, and various patients who have undergone the procedure and written to the agency

Background

Prostate cancer is the most common cancer seen in men and is the second most common cause of cancer deaths in men, trailing lung cancer. According to the American Cancer Society, adenocarcinoma of the prostate accounts for 47% of all new cancers detected in men, with an incidence of 330,000 cases per year. The number of cases is expected to increase dramatically over the next decade as a result of the aging of the population as well as improvements in, and access to, methods of diagnosis. Despite the high prevalence of this disease, the management of localized cancer remains controversial, with no standard clinical treatment algorithm. The two most common therapies are surgery (i.e., radical prostatectomy) and external beam radiotherapy. Within the past few years, brachytherapy and cryosurgery have gained attention as an alternative to surgery or radiation. Hormonal therapy is usually reserved for the symptomatic patient with systemic disease. Treatment and prognosis vary dependent upon the stage of cancer.

Table 1: Staging

Pathology	**TNM**
Digitally unrecognizable cancer	T1
<5% of turp specimen, low to medium grade	T1A
>5% of TURP specimen, or high-grade tumor	T1B
Tumor detected by elevated PSA	T1C
Digitally palpable cancer, organ confined	T2
<½ of one lobe	T2A
>½ of one lobe	T2B
Cancer extending beyond prostate capsule	T3
Metastases	N or M
To lymph nodes	N1-N3
Distant	M1-2

Cryosurgery is a technique that induces cell lysis in the prostate by direct application of low temperatures. Although cryosurgery of the prostate was introduced in the early 1960's, inability to control the freezing process led to unacceptable complications and the procedure was quickly abandoned. The present technique as it relates to prostate cancer was developed at Allegheny Hospital in Pittsburgh, PA in the early 1990's. More than 5000 procedures have been performed since 1991 when the FDA granted a 510k clearance.

The cost of cryosurgery is approximately $13,500. This compares to $14,200 for brachytherapy, $15,000 for external beam radiation and $10,600 for radical prostatectomy. Approximately 80 insurers offer some form of coverage; about 10% of insurers limit coverage to radiation failure. The overwhelming majority (>75%) of procedures are for primary treatment versus salvage.

Development of HCFA's Present Coverage Policy

Cryosurgery ablation of the prostate (CSAP) has been controversial. In August 1993, the American Urological Association published a position statement that CSAP is "investigational". This position made it increasingly difficult for providers and manufacturers to receive third party payment. There was no national policy by HCFA and thus there was significant carrier variation relating to coverage. HCFA first started to become involved in this topic in late 1994,when Cryomedical Sciences petitioned the agency to create a national coverage policy. In February 1995, Dr. Mark Stone, a medical officer at HCFA, informed Cryomedical Sciences that a national coverage policy could be established by either a randomized, prospective study being performed or the AUA changing their position statement. By spring, 1996, the AUA removed the experimental label from cryosurgery , stating: "cryosurgery is one of the methods of management of adenocarcinoma of the prostate. The long term curative efficacy of this treatment modality has not been established; when used, appropriate disclosure of facts of all other treatments should be made to the patient."

In August 1996 the Technical Advisory Committee (TAC) discussed the topic of cryosurgery of the prostate. Members reviewed the following articles:

Table 2: Articles reviewed at TAC, 1996

Chodak, G. Cryosurgery of the prostate revisited. *Cancer* 1993:72:1145-1146.

Cohen JK, Miller RJ, et al.. Cryosurgical ablation of the prostate: two-year prostate-specific antigen and biopsy results. *Urology* 1996:47:395-401.

Coogan CL and McKiel CF. Percutaneous cryoablation of the prostate: preliminary results after 95 procedures. *Journal of Urology* 1995;154:1813-1817.

Long, JP. Current status of cryosurgical ablation of the prostate. *Cope* 1996:May 32-35.

Miller RJ, Cohen JK, et al. Percutaneous, transperineal cryosurgery of the prostate as salvage therapy for post radiation recurrence of adenocarcinoma. *Cancer* 1996 77:1510-1514.

Shinohara K, Connolly J, Presti J, et al. Cryosurgical treatment of localized prostate cancer (stages T1 to T4):preliminary results *Journal of Urology* 1996:156:115-121

Wake RW, Hollabaugh RS, Bond KH. Cryosurgical ablation of the prostate for localized adenocarcinoma: a preliminary experience. *Journal of Urology* 1996:155:1663-1666.

Wieder J, Schmidt JD, Casola G, et al. Transrectal ultrasound-guided transperineal cryoablation in the treatment of prostate carcinoma: preliminary results. *Journal of Urology* 1996;154:435-441.

Appendix A lists the study design and outcomes of each study.

The TAC had several concerns with the studies presented. Specifically, they felt the weaknesses in the literature were: (1) heterogeneity in the study population (2) variability in technique (3) lack of control groups (4) short follow-up periods typically 24 months (5) lack of direct comparison to other methods of management for prostate cancer (6) large number of patients lost to follow-up (7) high risk of complications. Complications include impotence, incontinence, bladder outlet obstruction, fistula, strictures, and obstruction. There was also debate as to whether the measured endpoints are valid i.e., prostate specific antigen (PSA) and biopsy results may not accurately reflect morbidity or mortality.

The TAC consensus was that the evidence was insufficient to demonstrate the effectiveness and safety of cryosurgery for prostate cancer. Therefore, HCFA issued a press release in October 1996 that it would no longer cover cryosurgery ablation of the prostate. This noncoverage [*CIM 35-096*] went into effect April 15, 1997.

In addition, HCFA asked the National Cancer Institute and the AUA to consider co-sponsoring a multi-center study of this procedure. HCFA would agree to reimburse the medical service provided to Medicare beneficiaries within the study. HCFA also requested a technology assessment from Agency for Health Care Policy and Research (AHCPR) to assess data concerning cryoablation as a salvage therapy, for those persons who failed radiation therapy.

Recent Developments

With the passage of the 1997 Balance Budget Act and the need for HCFA to focus on revamping its entire Medicare coverage process, the conditional coverage idea of a jointly-sponsored multi-center study was abandoned. This decision was transmitted to Covance in September 1998; Covance (representing Endocare and several urologists) asked for reevaluation of all available literature and an opportunity to present new literature to the agency. This request was granted in October 1998.

Listed below are the articles recently reviewed by staff that were not previously discussed at the TAC meeting.

Table 3 Articles reviewed since TAC assessment

Bahn DK, Lee F, Solomon MH, et al. Prostate cancer: us-guided percutaneous cryoablation. *Radiology* 1995;194:551-556.

Benoit RM, Cohen JK, and Miller RJ. Comparison of the hospital costs for radical prostatectomy and cryosurgical ablation of the prostate. *Urology* 1998;52:820-824.

Carroll PR, Presti JC, Small E, and Roach M. Focal therapy for prostate cancer 1996: maximizing outcome. *Urology* 1997;49:84-94.

Chin JL, Downey DB, Mulligan M, and Fenster A. Three-dimensional transrectal ultrasound guided cryoablation for localized prostate cancer in nonsurgical candidates. *Journal of Urology* 1998;159:910-914.

Connolly JA, Shinohara K, Presti JC, and Carroll PR. Prostate-specific antigen after cryosurgical ablation of the prostate. *Urologic Clinics of North America* 1997;24:415-420.

Lee F, Bahn DK, McHugh TA, et al. Cryosurgery of prostate cancer: use of adjuvant hormonal therapy and temperature monitoring. *Anticancer Research* 1997;17:1511-1516.

Long, JP. Is there a role for cryoablation of the prostate in management of localized prostate carcinoma. *Hematology/Oncology Clinics of North America* 1996;10:675-689.

Long JL, Fallick ML, Larock DR, and Rand W. Preliminary outcomes following cryosurgical ablation of the prostate in patients with clinically localized prostate carcinoma. *Journal of Urology* 1998;159:477-484.

Schmidt JD, Doyle J, Larison. Prostate cryoablation: update 1998. *Ca Cancer J Clin* 1998;48:239-253.

Shinohara K, Rhee B, Presti, and Carroll PR. Cryosurgical ablation of prostate cancer: patterns of cancer recurrence. *Journal of Urology* 1997;158:2206-2210.

Wong WS, Chinn DO, et al. Cryosurgery as a treatment for prostate carcinoma: results and complications. *Cancer* 1997;79:963-974.

Bahn D, Lee F, et al. Transrectal ultrasound-guided cryosurgical ablation of prostate cancer: five year actuarila followup. Presented at AUA Meeting, November 1998.

Badalament RA, Bahn DK, Kim H, et al. Patient-reported complications after cryoablation therapy for prostate cancer. Accepted for publication in *Urology* 1999.

Chinn DC, Wong W, Chinn M. Temperature monitored prostate cryosurgery: five year experience. Submitted AUA Meeting, Dallas, 1999.

Appendix B lists the study design and outcomes of each study.

In general, these studies show that cryosurgery is an effective treatment for those patients with localized prostate cancer. Data shows that a significant number of patients are able to sustain undetectable levels of PSA for a period of time of at least 24 months. In addition, there is consistency across studies demonstrating a negative biopsy at two years often exceeding 80%. This compares favorably with the biopsy data following external beam irradiation.

In addition, the number of complications has also decreased significantly with the creation of new urethral warmers as well as improvement in technique such as use of ultrasound guidance. Keep in mind that as patients get older, patients become more prone to surgical complications of radical prostatectomy. As the technique continues to improve, the complication profile of cryosurgery becomes more similar to other technologies.

It is important to acknowledge that the scientific literature related to treatment of prostate cancer has flaws. There are few randomized trials, few patients enrolled in studies, and differences in outcome measures. For instance, the radiation oncology literature typically uses PSA < 1.0 ng/mL as evidence of a disease-free state whereas cryosurgery usually uses < 0.4 mg/mL as evidence of absence of disease. If one were to use PSA < 1.0 ng/mL as the reference in cryosurgical studies, cryosurgery would be more effective in obtaining PSA values less than 1.0 ng/mL. In addition, the technique used in radiation therapy has evolved over the past few years; therefore, the five year rates quoted in other therapies do not accurately reflect the treatment technology that exists today. The data exhibited by cryosurgery at this point is as effective as other technologies demonstrated early-on.

Of note, several providers who were lukewarm on cryosurgery have now become supportive. For instance, Dr. Fred Lee who is a prominent radiologist performing cryosurgery stated in 1995 that data was not clear. Three years later, he now believes the data is compelling and has opined a letter to the agency stating such. In 1996, Dr. John Long, a urologist from Boston, wrote that this technique was investigational. By 1998, Dr. Long has become one of cryosurgery's strongest supporters and has presented data to the agency that is outlined later in this memo.

By early October 1998 AHCPR had finished its assessment of cryosurgery as salvage therapy for those patients who had previously undergone radiation. This assessment concluded that although "cryosurgery has resulted in the biochemical disease-free survival of some patients who have had recurrent prostate cancer following radiation therapy, the effectiveness in salvaging such patients remains unclear because the number of patients treated has been small and the follow-up periods have been relatively short".

On December 9, 1998, John P. Long, MD, Director of Urologic Oncology and Assistance Professor of Medicine, Tufts University, New England Medical Center, presented pooled data from several studies. In data soon to be published, Dr. Long showed that current 5-year biochemical free survival outcomes for cryosurgery exceed 70%, which is comparable to radiotherapy and brachytherapy. A study of 206 patients had a 5-year biochemical survival of 78% for stages T1-T2. In a pooled retrospective analysis of 988 patients treated with cryosurgery from 5 institutions from 1993-1998, 82% of biopsies were negative. In addition, in a review of 445 consecutive patients with localized prostate cancer who received cryosurgery as primary therapy, conducted by Balm and Lee in Michigan, five year actuarial biopsy-proven disease free rate was 79%. Biochemical disease-free rate at the PSA < 0.5 ng/mL threshold was 76% for T1-T2 and 56% for T3-T4. This compares favorably to other therapies. In a study by Chinn in California, he calculated actuarial disease-free rates for 83 patients with localized prostate cancer who underwent cryosurgery, demonstrating an 80% disease-free state.

DECISION :

(1) Approve coverage as primary treatment for clinically localized prostate cancer. (Stages T1-T3)

(2) Continue noncoverage for salvage therapy for local failures after radical prostatectomy, external beam irradiation, and brachytherapy

The Cover Issues Manual 35-96 will be modified to reflect this change in policy.

Cryosurgery is safe, effective, as well as medically necessary and appropriate in certain patient populations specifically, those patients with Stages T1-T3 prostate cancer. It has demonstrated effectiveness through an absolute analysis as well as through a comparative analysis. Its results are comparable to brachytherapy and external beam radiation.

Cryosurgery has not yet been proven to be effective in all cases. The specific coverage policy is restricted to those patients who are undergoing this procedure as **primary therapy for clinically localized prostate cancer**. Localized prostate cancer is defined as Stages T1-T3. [See Table I]

The national noncoverage policy will remain intact for salvage therapy. Although such patients often have few options and may actually be the most likely to benefit from this technique, the data still does not clearly support its effectiveness and appropriateness. As more data becomes available, this decision will be reviewed.

Authors/Year	Type of Study	Outcomes Studied	Number of Patients	Patient Characteristic	Results	Clinical Applications
Long, JP, Fallick ML, et al. *Journal of Urology* 1998	Case Series	Serum PSA changes, random prostate biopsies	145 patients avg followup 36 months	Average age 65.6 years clinical stages T1 -T3	Actuarial rate for PSA <0.3 at 42 months was 59%. Crude rate at 24 months was 73%. Of 160 biopsies, 84% no cancer. 85% no clinical morbidity	Short-term outcomes for cryosurgery comparable to external beam radiotherapy.
Chin JL, Downey DB, Mulligan M, and Fenster	Case series	Serum PSA levels at 6 months	52 patients	Average age: 62 years		

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Journal of Urology 1998 Canada		Prostate biopsy at 3, 6, 12, 24 months	Followup ranged from 1-30 months.	Stages T1-T3 45 failed radiotherapy 7 deemed nonsurgical candidates	At 6 months, 11 patients had PSA <0.2. Numerous patients lost to followup. Minimal statistical testing performed. Only 70% of scheduled biopsies were performed	3d transrectal ultrasound appears to be feasible and worthwhile. Results similar to other studies. However, limited followup.
Wong WS, Chinn DO, et al. *Cancer* 1997 California		PSA levels at 3, 6, 12, 18, 24, and 30 months Biopsies at 3-6,12-18, and 24 months.	83 patients 98% patients were followed up.	Average age 69 years Clinical stages II-IV	Median PSA dropped by 95% to 0.3 ng/mL 30 months after surgery. At 24 months, 92% negative biopsy. Negative biopsies 90% for pts who had temp monitoring. Negative biopsy only 17% for patients who had no temp monitoring.	Importance of temp monitoring noted. Significant negative biopsy results as well as biochemical evidence of disease-free state.
Bahn DK, Lee F, Solomon MH *Radiology* 1995 Michigan	Case series	Biopsy at 3, 6, 12 months PSA levels at 3, 6, 12 months	210 patients	Average age: 67 years Localized prostate CA [diff staging system used] Mean PSA preop 12.6	Negative biopsy at 12 months 97% Mean PSA decreased from 12.6 to 0.43 at 12 months	Number of patients in disease free state at 12 months is impressive.
Shinohara K, Rhee B, Presti, and Carroll PR. *Journal of Urology* 1997 California	Case series	PSA levels at 3,6,12 months and every 6 months thereafter Biopsy at 6 months or with evid of biochemical failure	134 patients Mean followup: 17.6 months (range 3-36 months)	Average age: not specified Preop PSA ranged from 0.9 to 158 [avg19] Staging T1-T4	4/4 patients had undetectable PSA and negative biopsy at 36 months. 87% patients undetectable PSA and 98% negative biopsy rate at 12 months.	Determined what PSA levels indicate low risk of recurrence. Neoadjuvant androgen blockade helpful for T-T2. PSA nadir of 0.4 should be obtained post cryo. Failures more often at apex and seminal vesicles.

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